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WILSON DISEASE-AN OVERVIEW

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ABSTRACT

Wilson disease is a rare inherited disorder that prevents the body from getting rid of extra copper. Our body needs a small amount of copper from food to stay healthy. Too much copper is poisonous. The condition is due to mutations in the Wilson disease protein (*ATP7B*) gene. Normally liver releases extra copper into bile. With Wilson disease, the copper builds up in liver and it releases the copper directly into bloodstream. This can cause damage to brain, kidneys and eyes. Wilson disease is present at birth, but symptoms usually start between ages 5 and 35. It first attacks the liver, the central nervous system or both. The most characteristic sign is a rusty brown ring around the cornea of the eye. A physical exam and laboratory tests can diagnose it. Treatment is with drugs to remove the extra copper from body. It needs to take medicine and follow a low-copper diet for the rest of life. WD is treated with medication that reduces copper absorption or removes the excess copper from the body, but occasionally a liver transplant is required. A single abnormal copy of the gene is present in 1 in 100 people, who do not develop any symptoms (they are carriers). If a child inherits the gene from both parents, the child may develop Wilson's disease. Wilson's disease occurs in 1 to 4 per 100,000 people.

KEYWORDS: Wilson's disease mutation,autosomal.

INTRODUCTION

The disease bears the name of the British physician Samuel Alexander Kinnier Wilson (1878–1937), a neurologist who described the condition, including the pathological changes in the brain and liver, in 1912. Wilson's work had been predated by and drew on, reports from German neurologist Carl Westphal (in 1883), who termed it "pseudosclerosis"; by the British neurologist William Gowers (in 1888); and by Adolph Strümpell (in 1898), who noted hepatic cirrhosis. Neuropathologist John Nathaniel Cumings made the link with copper

accumulation in both the liver and the brain in 1948. The occurrence of hemolysis was noted in 1967. Cumings and simultaneously the New Zealand neurologist Derek Denny-Brown, working in the United States, first reported effective treatment with metal chelator. British anti-Lewisite in 1951. The first effective oral chelation agent, penicillamine, was discovered in 1956 by British neurologist John Walshe. In 1982, Walshe also introduced trientine, and was the first to develop tetrathiomolybdate for clinical use. Zinc acetate therapy initially made its appearance in the Netherlands, where physicians Schouwink and Hoogenraad used it in 1961 and in the 1970s, respectively, but it was further developed later by Brewer and colleagues at the University of Michigan.

DEFINITION

Wilson's disease or **hepatolenticular degeneration** is an autosomal recessive genetic disorder in which copper accumulates in tissues; this manifests as neurological or psychiatric symptoms and liver disease. The genetic defect causes excessive copper accumulation in the liver or brain.

EPIDEMIOLOGY

Wilson disease is found worldwide, with an estimated prevalence of 1 case per 30,000 live births in most populations. Approximately 1 person in 90 carries an abnormal ATP7B gene. However, in some populations, the prevalence is much higher. One of the highest reported prevalences was from a small mountain village on the island of Crete, where Wilson disease was diagnosed in 1 in 15 births. The increased prevalence was likely due to high rates of consanguinity in the isolated area. WD is present in most populations worldwide, and particularly in those in which consanguineous marriage is common. Some studies suggest that men and women are equally affected, though women are more likely than men to develop acute liver failure due to Wilson disease.

ETIOLOGY

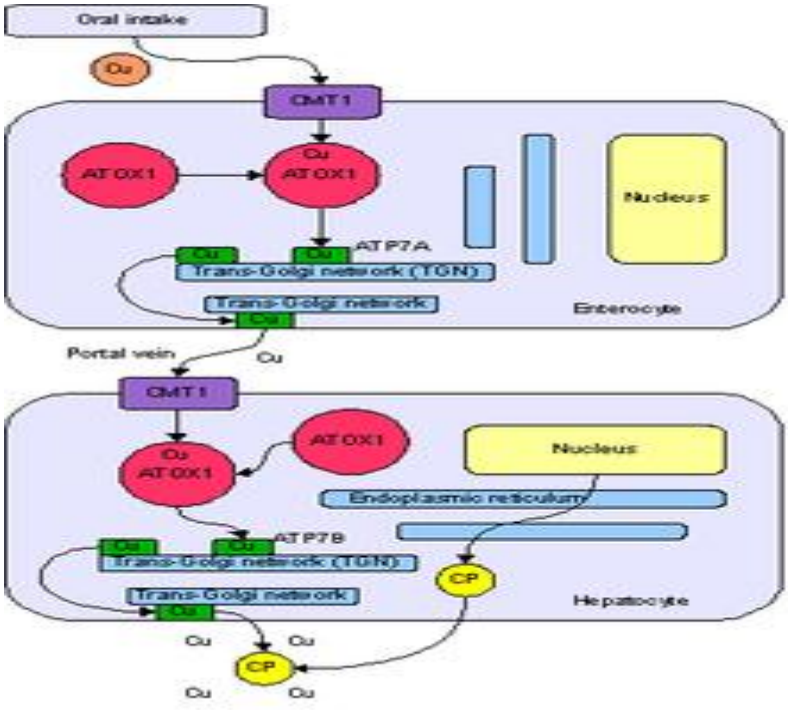
The normal estimated total body copper content is 50-100 mg and the average daily intake 2-5 mg, depending on an individual’s intake of legumes, meats, shellfish and chocolate. Copper is an important component of several metabolic enzymes, including lysyl oxidase, cytochrome c oxidase, superoxide dismutase and dopamine beta-hydroxylase.

Around 50-75% of intestinal copper is absorbed and then transported to the hepatocytes. This pathway is intact in Wilson disease. After copper reaches the hepatocyte, it is incorporated

into copper-containing enzymes and copper-binding proteins (CBPs), including ceruloplasmin, a serum ferroxidase. After 6 months, positive staining of CBPs for copper is almost exclusively found in association with liver diseases such as Wilson disease, chronic biliary disorders, cirrhosis/extensive fibrosis, and primary liver tumors.

In Wilson disease, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired. The transport of copper by the copper-transporting P-type ATPase is defective in Wilson disease. The excess copper resulting from Wilson disease promotes free radical formation that results in oxidation of lipids and proteins. Ultrastructural abnormalities in the earliest stages of hepatocellular injury, involving the endoplasmic reticulum, mitochondria, peroxisomes and nuclei, have been identified. Initially, the excess copper accumulates in the liver, leading to damage to hepatocytes. Eventually, as liver copper levels increase, it increases in the circulation and is deposited in other organs.

PATHOPHYSIOLOGY



Normal absorption and distribution of copper. Cu = copper, CP = ceruloplasmin, green = ATP7B carrying copper.

Copper is needed by the body for a number of functions, predominantly as a cofactor for a number of enzymes such as ceruloplasmin, cytochrome c oxidase, dopamine β-hydroxylase, superoxide dismutase and tyrosinase.

Copper enters the body through the digestive tract. A transporter protein on the cells of the small bowel, copper membrane transporter 1 (CMT1), carries copper inside the cells, where some is bound to metallothionein and part is carried by ATOX1 to an organelle known as the trans-Golgi network. Here, in response to rising concentrations of copper, an enzyme called ATP7A releases copper into the portal vein to the liver. Liver cells also carry the CMT1 protein and metallothionein and ATOX1 bind it inside the cell, but here it is ATP7B that links copper to ceruloplasmin and releases it into the bloodstream, as well as removing excess copper by secreting it into bile. Both functions of ATP7B are impaired in Wilson's disease. Copper accumulates in the liver tissue; ceruloplasmin is still secreted, but in a form that lacks copper (termed apoceruloplasmin) and is rapidly degraded in the bloodstream.

When the amount of copper in the liver overwhelms the proteins that normally bind it, it causes oxidative damage through a process known as Fenton chemistry; this damage eventually leads to chronic active hepatitis, fibrosis (deposition of connective tissue) and cirrhosis. The liver also releases copper into the bloodstream that is not bound to ceruloplasmin. This free copper precipitates throughout the body but particularly in the kidneys, eyes and brain. In the brain, most copper is deposited in the basal ganglia, particularly in the putamen and globuspallidus (together called the *lenticular nucleus*); these areas normally participate in the coordination of movement as well as playing a significant role in neurocognitive processes such as the processing of stimuli and mood regulation. Damage to these areas, again by Fenton chemistry, produces the neuropsychiatric symptoms seen in Wilson's disease.

CLINICAL MANIFESTATIONS

Wilson's disease causes a wide variety of signs and symptoms that are often mistaken for other diseases and conditions. Signs and symptoms vary depending on what parts of your body are affected by Wilson's disease. The clinical manifestations of Wilson disease are predominantly hepatic, neurologic and psychiatric, with many patients having a combination of symptoms. Hemolysis is also a common finding in patients with acute liver failure due to Wilson disease.

Liver disease

Liver disease may present itself as tiredness, increased bleeding tendency or confusion (due to hepatic encephalopathy) and portal hypertension which leads to esophageal varices, blood vessels in the esophagus that may bleed in a life-threatening fashion, as well as enlargement

of the spleen (splenomegaly) and accumulation of fluid in the abdominal cavity (ascites). On examination, signs of chronic liver disease such as spider angiomata (small distended blood vessels, usually on the chest) may be observed. Chronic active hepatitis has caused cirrhosis of the liver in most by the time they develop symptoms.

Neuropsychiatric symptoms

About half the people with Wilson's disease have neurological or psychiatric symptoms. Most initially have mild cognitive deterioration and clumsiness, as well as changes in behavior. Specific neurological symptoms usually then follow, often in the form of parkinsonism with or without a typical hand tremor, masked facial expressions, slurred speech, ataxia (lack of coordination) or dystonia (twisting and repetitive movements of part of the body). Seizures and migraine appear to be more common in Wilson's disease. A characteristic tremor described as "wing-beating tremor" is encountered in many people with Wilson's.

Cognition can also be affected in Wilson's disease. Frontal lobe disorder, impaired judgement, promiscuity, apathy and executive dysfunction with poor planning and decision making) and subcortical dementia (may present as slow thinking, memory loss and executive dysfunction, without signs of aphasia, apraxia or agnosia)may occur.

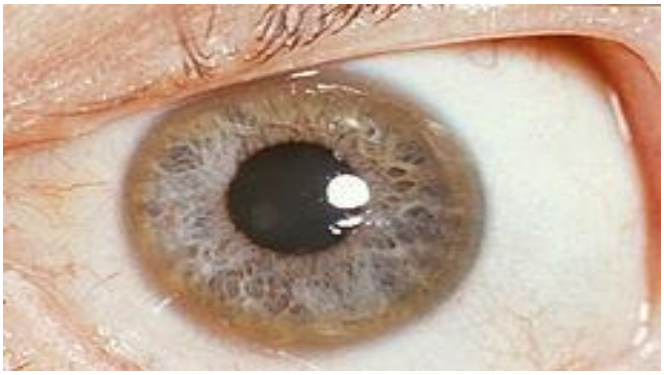
Psychiatric problems due to Wilson's disease may include behavioral changes, depression, anxiety and psychosis. Psychiatric symptoms are commonly seen in conjunction with neurological symptoms and are rarely manifested on their own.

Other organ systems

Medical conditions have been linked with copper accumulation in Wilson's disease:

- **Eyes:Kayser–Fleischer rings (KF rings)**

A pathognomonic sign, may be visible in the cornea of the eyes, they are due to copper deposition in Descemet's membrane. They do not occur in all people with Wilson's disease. Wilson's disease is also associated with sunflower cataracts exhibited by brown or green pigmentation of the anterior and posterior lens capsule. Neither cause significant visual loss. KF rings occur in approximately 66% of diagnosed cases.



- **Renal tubular acidosis**

A disorder of bicarbonate handling by the proximal tubules leads to nephrocalcinosis (calcium accumulation in the kidneys), a weakening of bones (due to calcium and phosphate loss) and occasionally aminoaciduria (loss of essential amino acids needed for protein synthesis), hypercalciuria, microscopic hematuria and/or minimal proteinuria.

- **Hypoparathyroidism:** Failure of the parathyroid glands leading to low calcium levels, infertility and habitual abortion.

- **Hematological:** Acute non-immunological hemolytic anemia due to oxidative injury of the cell membrane caused by excess copper and epistaxis.

- **Orthopedic:** Chondrocalcinosis, osteoarthritis, metabolic bone disease, juvenile polyarthritis, recurrent fracture and dislocation.

- **Cardiovascular:** Arrhythmias, rheumatic-fever-like manifestation, Weakness of the heart muscle is a rare but recognized problem in Wilson's diseas.

- **Gynecological:** Primary or secondary amenorrhea, repeated and unexplained spontaneous abortions.

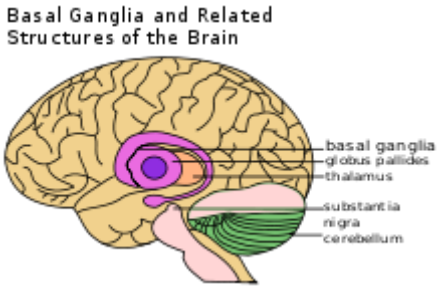
- **Skeletal system:** Skeletal abnormalities in patients with Wilson disease widely vary and include osteoporosis, osteomalacia, rickets, spontaneous fractures and polyarthritis.

- **Skin:** Skin pigmentation and a bluish discoloration at the base of the fingernails (azure lunulae) have been described in patients with Wilson disease.

DIAGNOSIS AND MONITORING

The main sites of copper accumulation are the liver and the brain and consequently liver disease and neuropsychiatric symptoms are the main features that lead to diagnosis. People with liver problems tend to come to medical attention earlier, generally as children or teenagers, than those with neurological and psychiatric symptoms, who tend to be in their twenties or older.

Diagnosis



Location of the basal ganglia, the part of the brain affected by Wilson's disease.

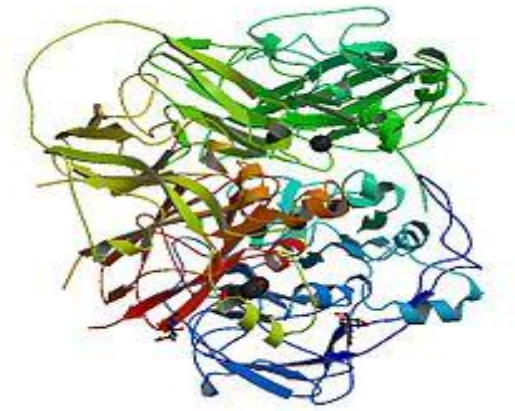
There is no totally reliable test for Wilson's disease, but levels of ceruloplasmin and copper in the blood, as well of the amount of copper excreted in urine during a 24-hour period, are together used to form an impression of the amount of copper in the body. The gold standard or most ideal test is a liver biopsy.

The diagnosis of Wilson disease is made by relatively simple tests. The tests can diagnose the disease in both symptomatic patients and people who show no signs of the disease.

These tests can include

- Ophthalmologic slit lamp examination for Kayser-Fleischer rings.
- Serum ceruloplasmin tests
- 24 hr urine copper test
- Liver biopsy for histology and histochemistry and copper quantification.
- Genetic testing, haplotype analysis for siblings and mutation analysis.

Ceruloplasmin



Ceruloplasmin

Measurement of the serum ceruloplasmin level is important. Normal values, which range from 200 to 400 mg/l, Levels of ceruloplasmin are abnormally low (<0.2 g/L) in 80–95% of cases Low ceruloplasmin is also found in Menkes disease and aceruloplasminemia, which are related to, but much rarer than Wilson's disease.

Serum ceruloplasmin levels are low in newborns and gradually rise within the first 2 years of life. Approximately 90% of all patients with Wilson disease have ceruloplasmin levels of less than 20 mg/dL (reference range, 20-40 mg/dL). (Ceruloplasmin is an acute phase reactant and may be increased in response to hepatic inflammation, pregnancy, estrogen use, or infection.) Falsely low ceruloplasmin levels may be observed in any protein deficiency state, including nephrotic syndrome, malabsorption, protein-losing enteropathy and malnutrition. Ceruloplasmin levels may also be decreased in 10-20% of Wilson Disease gene heterozygotes, who do not develop Wilson disease and do not require treatment.

❖ **Serum and urine copper**

Serum copper is paradoxically low but urine copper is elevated in Wilson's disease. Urine is collected for 24 hours in a bottle with a copper-free liner. Levels above 100 µg/24h (1.6 µmol/24h) confirm Wilson's disease and levels above 40 µg/24h (0.6 µmol/24h) are strongly indicative. In children, the penicillamine test may be used. A 500 mg oral dose of penicillamine is administered and urine collected for 24 hours. If this contains more than 1600 µg (25 µmol), it is a reliable indicator of Wilson's disease. This test has not been validated in adults.

❖ **Hepatic copper concentration**

This test is regarded as the criterion standard for diagnosis of Wilson disease. A liver biopsy with sufficient tissue reveals levels of more than 250 mcg/g of dry weight even in asymptomatic patients. Special collection vials are available to help avoid contamination.

❖ **Radiolabeled Copper**

Radiolabeled copper testing directly assays hepatic copper metabolism. Blood is collected at 1, 2, 4, 24 and 48 hours after oral ingestion of radiolabeled copper (^{64} Cu or^{67} Cu) for radioactivity in serum. In all individuals, radioactivity promptly appears after absorption, followed by hepatic clearance. In healthy people, reappearance of the radioactivity in serum occurs as the labeled copper is incorporated into newly synthesized ceruloplasmin and released into the circulation.

❖ **Liver biopsy**

Once other investigations have indicated Wilson's disease, the ideal test is the removal of a small amount of liver tissue through a liver biopsy. This is assessed microscopically for the degree of steatosis and cirrhosis and histochemistry and quantification of copper are used to measure the severity of the copper accumulation. A level of 250 μg of copper per gram of dried liver tissue confirms Wilson's disease. Occasionally, lower levels of copper are found; in that case, the combination of the biopsy findings with all other tests could still lead to a formal diagnosis of Wilson's.

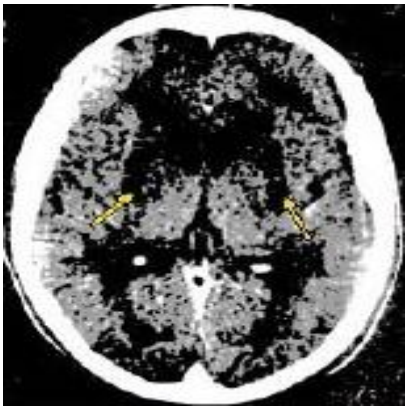
❖ **Genetic testing**

Mutation analysis of the *ATP7B* gene, as well as other genes linked to copper accumulation in the liver, may be performed. Once a mutation is confirmed, it is possible to screen family members for the disease as part of clinical genetics family counseling.

With a diagnosis of WD, it is mandatory to counsel family members on the importance of biochemical or genetic screening of siblings and other family members, to identify those who might be presymptomatic gene mutation carriers. The probability of family members of an affected individual being similarly affected (carrying two mutated genes) is 25% for siblings and 0.5% for offspring.

❖ **Cranial CT Scanning**

The cranial lesions observed on CT scans are typically bilateral and are classified into 2 general categories: (1) well-defined, slitlike, low-attenuation foci involving the basal ganglia, particularly the putamen and (2) larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus.



Computed tomography (CT) scan in a 15-year-old boy who presented with central nervous system findings consistent with Wilson disease.

PET Scanning

Positron emission tomography (PET) scanning reveals a significantly reduced regional cerebral metabolic rate of glucose consumption in the cerebellum, striatum and to a lesser extent, in the cortex and thalamus.

PET scan analyses of patients with Wilson disease have also demonstrated a marked reduction in the activity of dopa-decarboxylase, indicative of impaired function of the nigrostriatal dopaminergic pathway.

Electron microscopy

Electron microscopic studies on ultrathin sections reveal numerous electron-dense lysosomes and residual bodies. The electron microscopic detection of copper-containing hepatocytic lysosomes is helpful in the diagnosis of the early stages of Wilson disease, in addition to the quantification of hepatic copper by atomic absorption spectrophotometry

Genetics

Wilson's disease has an autosomal recessive pattern of inheritance. In order to inherit it, both of the parents of an individual must carry an affected gene. Most have no family history of

the condition. People with only one abnormal gene are called carriers (heterozygotes) and may have mild, but medically insignificant, abnormalities of copper metabolism.

DIFFERENTIAL DIAGNOSIS OF WILSON'S DISEASE (NOTED USUALLY IN PATIENTS BELOW 50 YEARS OF AGE).

Presentation	Differential diagnosis
Parkinsonian features	Juvenile Parkinson's disease Neurodegeneration with brain iron accumulation (NBIA)
Dystonia	Dopa-responsive dystonia Idiopathic torsion dystonia Lipid storage disease Post-encephalitic dystonia Dystonic cerebral palsy Focal dystonias such as writer's cramp
Ataxia	Degenerative or metabolic cerebellar disease Demyelinating disease Craniovertebral anomaly
Titubation or tremor	Degenerative cerebellar disease Demyelinating disease Essential tremor
Myoclonus and cognitive deterioration	Mitochondrial disease Neuronal ceroidlipofuscinosis Lafora's bodies disease Baltic myoclonus Subacutesclerosingpanencephalitis (SSPE)
Chorea	Huntington's disease Sydenham's chorea Storage disorders Drug-induced chorea Neuroacanthocytosis Vasculitis (particularly systemic lupus erythematosus)
Psychiatric illness	Major psychosis Attention deficit hyperactive disorder Personality disorder Mental retardation
Proximal muscle weakness	Muscular dystrophy Metabolic myopathy Inflammatory myopathy
Liver disease	Acute hepatitis of unknown etiology Acute fulminant hepatic failure of unknown etiology Chronic active hepatitis of unknown etiology Cirrhosis of liver of unknown etiology

SCREENING FAMILY MEMBERS OF PATIENTS WITH WILSON'S DISEASE

Tests	Homozygous or compound heterozygous		Heterozygous carrier	Non-carrier
	Symptomatic	Presymptomatic		
[a]Commonly used tests for family screening. Abbreviation: KF, Kayser–Fleischer.				
Clinical examination[a]	Might have either early hepatic or neurological features	Hepatomegaly in 38% of cases	No apparent clinical abnormality	Normal
Slit lamp examination for KF ring[a]	Commonly positive in neuropsychiatric presentations and in 50% of hepatic presentation	Positive KF ring in about 1/3 of cases	Usually negative	Negative
Serum ceruloplasminlevel[a]	Low in about 85% of cases	Same as symptomatic	Low (<15 mg%) in about 15–20% of cases	Normal
Genetic analysis (haplotypic)[a]	Mutation in both Wilson's disease genes	Same as symptomatic	Abnormal mutation in one gene	No mutational change
24-hour urinary copper excretion	Usually high (>100 μg)	Same as symptomatic	Normal	Normal (20–50 μg)
Neuroimaging of brain	Commonly abnormal in neuropsychiatric presentation	Abnormal in 25% of cases	Normal	Normal

TREATMENT

PHARMACOLOGICAL TREATMENT

Medication

Medical treatments are available for Wilson's disease. Some increase the removal of copper from the body, while others prevent the absorption of copper from the diet. The mainstay of therapy for Wilson disease is the use of chelating agents and medications that block copper absorption from the gastrointestinal (GI) tract.

Zinc and penicillamine are lifelong medications for patients with Wilson disease. Dosages vary with the severity of the disorder. Another chelating agent is **trientine,** which may be more easily tolerated than penicillamine. Patients who do not respond to zinc therapy and

who have increased activities of liver enzymes should be identified so that chelating agents may be added to the therapeutic regimen.

Other medications used to treat Wilson disease include

- Anticholinergics
- Baclofen
- Gamma-aminobutyric acid (GABA) antagonists
- Levodopa to treat parkinsonism and dystonia symptoms
- Antiepileptics to treat seizures
- Neuroleptics to treat psychiatric symptoms.
- Lactulose used to treat hepatic encephalopathy.

- **Chelating agents**
- Copper chelating agents are the first-line therapy for WD. In the initial phase of treatment, toxic levels of copper are controlled, and dietary copper is restricted. Chelating agents are therefore prescribed to promote 24-hour excretion of approximately 2 mg of copper in the urine, to induce a negative copper balance. In the maintenance phase, the dosage can be reduced and zinc salt added to prevent the systemic absorption of copper.

- After the initiation of therapy with a chelating agent, the patient needs to be aware of potential adverse effects of the agents with which he or she is being treated. For instance, some of the concerning adverse effects are those commonly associated with penicillamine use. In addition, a patient must also be aware of the potential to develop worsening of some symptoms when chelation is started; in particular, patients with neurologic signs and symptoms can see worsening of these with chelation and in some instances, therapy needs to be reduced or stopped. Laboratory tests in patients started on penicillamine should include hematology and biochemical monitoring, as well as urinalysis. Perform a physical examination, 24-hour urinary copper excretion assay, complete blood count (CBC), urinalysis, serum free copper measurement and renal and liver function tests on a weekly basis for the first 4-6 weeks following initiation of chelation therapy.

The best way to monitor efficacy is to measure serum nonceruloplasmin-bound copper. This is measured by the following formula: Total serum copper (mcg/dL) - 3[ceruloplasmin (mg/dL)]. The reference range is less than 15 mcg/dL.

An adjunctive way to monitor efficacy is to measure urinary copper excretion. Urinary chelator levels usually measure 200-500 mcg/day. Urinary zinc levels usually measure less than 75 mcg/day.

Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter. In patients with Kayser-Fleischer rings, a yearly slit-lamp examination should document fading or disappearance if patients are being adequately "decoppered."

Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease. Frequent follow-up with patients is necessary.

❖ **Penicillamine**

- Brand name: Cuprimine, Depen.
- Class: Chelators.
- Dose : 250 mg PO QID; dosage range 500-1500 mg/day.
- Pregnancy: Not to exceed 500-750 mg/day. Planned cesarean section, Reduce dose to 250 mg/day for the last 6 weeks of pregnancy and postoperatively until wound healing completed.
- Dosing considerations.
  - Adjust dose to achieve urinary copper excretion of 0.5-1 mg/day.
- Free copper levels in serum: Maintain at <10 mcg/dL.
- Rarely used because of deep IM injection of 2-3 mL that is painful, 2.5-3 mg/kg IM BID/TID.

Other Information

Preadministered antihistamine may decrease side effects.

Other Indications & Uses

- Do not use in iron, cadmium, or selenium due to formation of toxic complexes.

MOA: This binds copper (chelation) and leads to excretion of copper in the urine. Hence, monitoring of the amount of copper in the urine can be done to ensure a sufficiently high dose is taken.

- D-penicillamine not only chelates copper from tissue, but also detoxifies tissue copper by promoting the synthesis of metallothionein, which forms a non-toxic combination with copper.

Adverse Effects

- Fever, 30% of children (frequent)
- Tightness sensation, Chest, limbs, jaw, abdomen
- Hypertension (frequennt, dose related)
- Tachycardia (frequent, dose related)
- Injection site pain, abscess
- Nausea/Vomiting
- Headache
- Paresthesia (hand)
- Tremor
- Blepharospasm
- Conjunctivitis
- Lacrimation
- Nasal discharge
- Nephrotoxicity
- During administration of D-penicillamine, periodic clinical, hematological, biochemical (transaminases) and routine urinary parameters are monitored weekly for 1 month, then monthly for 6 months and at 6-monthly intervals thereafter. An improvement in clinical features is usually noted after 2–3 months, continuing over a period of 1–2 years. Regular measurement of the 24-hour urinary excretion of copper provides an important index of copper removal from the body. If the excretion level in a compliant patient decreases to less than 0.5 mg daily, the dose can be lowered. At this point, a zinc salt should be added to the treatment regimen, preferably before meals. D-penicillamine should be taken 2 hours after meals to avoid any interaction with the zinc.

- Pregnant women with WD can have a successful pregnancy while undergoing chelation therapy. These patients should continue on the same agent but with a slightly reduced dosage, particularly in the third trimester. Abrupt cessation of the drug treatment can be fatal. If the patient is completely free of toxic copper, she should be advised to take only zinc salt. Although D-penicillamine and trientine are potentially teratogenic, there are

currently insufficient data concerning their teratogenic effects in pregnant patients with WD to warrant cessation of treatment.

ANTI-COPPER DRUGS USED IN THE TREATMENT OF WILSON'S DISEASE

Drug	Mechanism of action	Dose	Toxicity
Zinc acetate	Blockage of copper absorption by inducing metallothionein in enterocytes	150 mg/day of elemental zinc in three divided doses	Mild abdominal discomfort in 10% of patients
Trientine	Chelation and urinary excretion of copper	1 g/day in three divided doses (range 750–2,000 mg)	Sideroblastic anemia. Autoimmune disorders same as D-penicillamine but occur less frequently
D-Penicillamine	Chelation and urinary excretion of copper	0.75–1.5 g/day (children: 20 mg/kg/body weight)	Initial neurological worsening, acute hypersensitivity, proteinuria. Delayed side effects: Goodpasture's syndrome, polymyositis, neuropathy and neuromuscular junction defect, systemic lupus erythematosus, bone marrow suppression effects on immune system, collagen and on skin during prolonged therapy (aging effect)
Ammonium tetrathiomolybdate	Complex with copper and protein within intestine and circulation, thereby detoxifying copper in plasma and blocking copper absorption from the intestine	2–3 mg/kg/body weight given in six doses along with meal and in the interval between meals	Overtreatment produces reversible anemia. Long-term safety and efficacy unknown

- **Trientine hydrochloride**
  - Trientine is considered to be safer alternatives to D-penicillamine. Trientine is a less potent copper remover than D-penicillamine, and its toxic profile is similar to that of D-penicillamine, although side effects are less frequent and generally milder.

❖ **Tetrathiomolybdate**

- A further agent, under clinical investigation, with known activity in Wilson's disease is tetrathiomolybdate. It can also considered an alternative to D-Penicillamine. Ammonium tetrathiomolybdate, an agent previously used to treat copper toxicosis in animals, has been advocated because of its lower toxic profile, but it is still an experimental drug that is not routinely available and its long-term safety and efficacy is unknown.

❖ **Zinc acetate**

Once all results have returned to normal, zinc (usually in the form of a zinc acetate prescription called Galzin) may be used instead of chelators to maintain stable copper levels in the body. Zinc stimulates metallothionein, a protein in gut cells that binds copper and prevents their absorption and transport to the liver. Zinc therapy is continued unless symptoms recur or if the urinary excretion of copper increases.

❖ **Dimercaprol**

In rare cases where none of the oral treatments are effective, especially in severe neurological disease dimercaprol is occasionally necessary. This treatment is injected intramuscularly (into a muscle) every few weeks and has unpleasant side effects such as pain.

COMPLICATIONS

- **Pregnancy**

Excessive intrauterine copper concentrations may be responsible for the high rate of spontaneous abortions in patients with Wilson disease. D-penicillamine (0.75-1.5 g/day) appears to pose no major risk to the fetus and should be continued throughout the pregnancy.

- **Pediatric**

Pediatricians should consider Wilson disease in any child with hepatic abnormalities. The initial tests should be performed and further workup by a pediatric gastroenterologist may be necessary if suspicion remains high.

- **Geriatric**

Almost all patients have significant hepatic and neuropsychiatric symptoms before reaching the geriatric age group. Patients with Wilson disease who are untreated will most likely present with fulminant hepatic failure or with signs and symptoms of cirrhosis in the geriatric population. Consideration for liver transplantation is less likely with advancing age.

- **Neurologic deterioration with treatment**

It is very important to recognize that some patients may develop worsening neurologic symptoms when therapy is initiated. In some of these instances, the chelating agent needs to be stopped and the patient should be run on zinc acetate alone. In patients on long-term treatment who show signs of progressive neurologic symptoms on chelating agents, medication compliance and dietary compliance require review, along with an assessment of the efficacy of laboratory testing.

- **Medicolegal concerns**

Medicolegal issues may arise if the diagnosis is not considered in the face of appropirate clues. Also critical is to provide the patient with information and to screen siblings of the index case for the possibility of Wilson disease, because the estimated frequency is 1 in 4 in situations in which the siblings have the same parents.

- **Consultations**

Consider consultation with gastroenterologists with specialty training in hepatology for any patient with Wilson disease, especially when evidence of hepatic insufficiency is present. Consultation with surgeons may be sought for liver transplantation when deemed necessary.

SYMPTOMATIC TREATMENT

Symptomatic treatment for dystonia and parkinsonian features, psychiatric disturbances, and encephalopathy can be very successful and reassuring for the patient with WD. The treatment of dystonia and parkinsonian features includes the administration of anticholinergics, tizanidine, baclofen, levodopa, or ɣ-aminobutyric acid (GABA) agonists—particularly clonazepam. Comparative studies of the use of these medications for symptomatic therapy are, however, lacking. Botulinum toxin injection is a useful adjunct therapy in cases with severe limb dystonias when other treatments are unsuccessful. Convulsions can be controlled with both traditional and newer antiepileptic drugs; in our opinion, more than one drug is often required to achieve control. Psychiatric disturbance is usually managed with atypical neuroleptics and occasionally with traditional neuroleptics. Hepatic encephalopathy is managed with a standard regimen of protein restriction and lactulose. Patients must avoid most alcohol consumption and potential hepatotoxic drug therapy.

NON PHARMACOLOGICAL TREATMENT

1) Dietary

- In general, a diet low in copper-containing foods is recommended.
- Patients should generally avoid eating foods with a high copper content, such as liver, chocolate, nuts, mushrooms, dry fruits, legumes and shellfish (especially lobster).
- Drinking water from atypical sources (eg, well water) should be analyzed for copper content and replaced with purified water if the copper content is greater than 0.2 parts per million.
- Patients should avoid from cooking or taking food from copper bowls and plates.

2) Physical therapy

- Physiotherapy is beneficial for patients with the neurologic form of the disease. The copper chelating treatment may take up to six months to start working, and physical therapy can assist in coping with ataxia, dystonia and tremors, as well as preventing the development of contractures that can result from dystonia.

3) Liver Transplantation

Liver transplantation is an effective cure for Wilson's disease but is used only in particular scenarios because of the risks and complications associated with the procedure. It is used mainly in people with fulminant liver failure who fail to respond to medical treatment or in those with advanced chronic liver disease. Liver transplantation is avoided in severe neuropsychiatric illness, in which its benefit has not been demonstrated. Hepatic transplantation is also indicated in the absence of liver failure in patients with neurological WD in whom chelation therapy has proved ineffective and significant improvements in neurological features have been reported, which include the disappearance of the KF ring.

PROGNOSIS

Left untreated, Wilson's disease tends to become progressively worse and is eventually fatal. With early detection and treatment, most of those affected can live relatively normal lives. Liver and neurologic damage that occurs prior to treatment may improve, but it is often permanent. Symptomatic WD patients require lifelong treatment, because an interruption to therapy or inadequate treatment can lead to fatalities within 9 months to 3 years. The severity of disease at the start of treatment determines the level of disability and an early onset is worse than a late onset in terms of prognosis. If treatment is begun early enough, symptomatic recovery is usually complete, leading to a normal life expectancy. Residual

dysarthria and mild dystonia are relatively common in neurological WD. Patients with a prognostic index (ie, score) of 7 or greater should be considered for liver transplantation (see Table below).

Table. Prognostic Index in Fulminant Wilsonian Hepatitis

Score	0	1	2	3	4
Serum bilirubin (reference range, 3-20 mmol/L)	< 100	100-150	151-200	201-300	>300
Serum aspartate transaminase (reference range, 7-40 IU/L)	< 100	100-150	151-200	201-300	>300
Prothrombin time prolongation (seconds)	< 4	4-8	9-12	13-20	>30

Prognosis after liver transplantation is relatively good.

CONCLUSION

Despite significant advances in our understanding of the disease process in WD, further insights into the intracellular processes involved in copper homeostasis would enhance our knowledge and allow for improved treatment. Reported variations in the disease phenotype of patients with the same set of mutations in the *ATP7B* gene suggest that the phenotype can be modulated by modifier genes such as *ATOX1* and *COMMD1*. New methods that provide faster and cheaper means of genotyping patients will speed up the process of confirmation of diagnosis in targeted population groups and DNA microarray analysis may help in the direct sdetection of the mutations. In terms of therapy, long-term clinical trials of recently advocated agents such as tetrathiomolybdate are needed to judge these treatments' efficacy, and a more comprehensive solution could involve gene therapy.

REFERENCES

1. Wilson SAK (1912) Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver: 295–509.
2. Cunning JN (1948) The copper and iron content of brain and liver in the normal and in hepatolenticular degeneration: 410–415.
3. Frommer DJ (1974) Defective biliary excretion of copper in Wilson's disease. 15: 125.
4. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML (2007). "Wilson's disease". Lancet, 369(9559): 397–408.
5. Kinnier Wilson SA (1912). "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver", 34(1): 295–507:10.1093/34.4.295.

6. Merle U, Schaefer M, Ferenci P, Stremmel W (2007). "Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study". (1): 115–20.
7. Lorincz MT (2010). "Neurologic Wilson's disease". Annals of the New York Academy of Sciences, 1184: 173–87.
8. Pagonabarraga, J; Goetz, C (2012). Biller, J, ed. Practical neurology (4th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Heath. p. 282.
9. Yanoff, Myron; Jay S. Duker (2008). Ophthalmology (3rd ed. ed.). Edinburgh: Mosby. p. 411.
10. Grubenbecher S, Stüve O, Hefter H, Korth C (2006). "Prion protein gene codon 129 modulates clinical course of neurological Wilson disease".
11. Roberts EA, Schilsky ML; Division Of Gastroenterology Nutrition (2003). "A practice guideline on Wilson disease". Hepatology, 37(6): 1475–92.
12. Lee, GR (1999). "Chapter 48: acquired hemolytic anaemias resulting from direct effects of infectious, chemical or physical agents". In Lee GR, Foerster J, Lukens J et al. Wintrobe's clinical hematology. vol 1 (10th ed.). Williams & Wilkins. p. 1298.
13. Shaver WA, Bhatt H, Combes B (1986). "Low serum alkaline phosphatase activity in Wilson's disease". Hepatology, 6(5): 859–63.
14. Das SK, Ray K (September 2006). "Wilson's disease: an update". Nat Clin Pract Neuro, l2(9): 482–93.
15. Walshe JM (July 1996). "Treatment of Wilson's disease: the historical background". QJM, 89(7): 553.
16. Brewer GJ, Askari FK (2005). "Wilson's disease: clinical management and therapy". Journal of Hepatology, 42(Suppl 1): 13–21.
17. Robertson WM (February 2000). "Wilson's disease". Arch. Neurol. 57(2): 276.
18. Cumings JN (1948). "The copper and iron content of brain and liver in the normal and in hepato-lenticular degeneration"(Dec): 410.
19. McIntyre N, Clink HM, Levi AJ, Cumings JN, Sherlock S (February 1967). "Hemolytic anemia in Wilson's disease". N. Engl. J. Med. 276(8): 439–444.
20. Cumings JN (March 1951). "The effects of B.A.L. in hepatolenticular degeneration". 74(1): 10–22.
21. Denny-Brown D, Porter H (December 1951). "The effect of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease)". N. Engl. J. Med. 245(24): 917–25.

22. Vilensky JA, Robertson WM, Gilman S (September 2002). "Denny-Brown, Wilson's disease and BAL (British antilewisite [2,3-dimercaptopropanol])". Neurology, 59(6): 914–6..
23. Walshe JM (January 1956). "Wilson's disease; new oral therapy". Lancet, 267 (6906).
24. Walshe JM (March 1982). "Treatment of Wilson's disease with trientine (triethylenetetramine) dihydrochloride". Lancet, 1(8273): 643–647.
25. Harper PL, Walshe JM (December 1986). "Reversible pancytopenia secondary to treatment with tetrathiomolybdate". Br. J. Haematol. 64(4): 851–853.